

Linde M, Hagen K et al. Onabotulinum toxin A treatment of cervicogenic headache: A randomised, double blind, placebo-controlled study. Cephalalgia 2011;31:797-807.

Design: Crossover randomized clinical trial

Population/sample size/setting:

- 28 patients (17 women, 11 men, mean age 46) treated for cervicogenic headache in a university neurology clinic in Norway
- Eligibility criteria were strictly unilateral headache at least 15 days per month, with neck involvement (restricted range of motion, provocation by movement/external pressure, pain radiation), and a positive nerve block of the greater occipital nerve
- Exclusion criteria were previous treatment with botulinum toxin, any litigation for head or neck trauma, cervical spinal stenosis, medical comorbidity (cancer, arthritis, systemic illness), frequent other headache which could not be distinguished from cervicogenic headache, and use of other headache prophylactic medication within past 4 weeks

Main outcome measures:

- All patients were injected with both botulinum toxin and with saline, with the order determined by a random process
- Injections of both botulinum toxin and saline were placed as fixed-site injections at the occipital muscle insertion, splenius capitis, upper trapezius, sternocleidomastoid, and levator scapulae; each muscle received 20U of botulinum toxin or equal volume of saline 100U of botulinum toxin total dose)
- After the first injection of botulinum toxin or saline, the patients were followed for 8 weeks, and received their second injections no sooner than 8 weeks after the first injection, but after the patient had reached $\geq 50\%$ of days with moderate to severe headache compared to baseline (the scheduling is ambiguous in the methods section of the study)
- Main outcome measure was the change in the mean weekly frequency of moderate to severe headache
 - o Several secondary measures were done, including headache intensity and duration, frequency of neck pain, analgesic use, and sick leave
- 28 patients were randomized; 13 received botulinum toxin as the first injection and 15 received saline as first injection
 - o 10 of the 13 botulinum toxin patients remained in the study and received saline as the second injection; 14 of the 15 saline patients remained in the study and received botulinum toxin as the second injection
- On the main outcome variable, the frequency of headache was reduced by 0.7 days/week with botulinum toxin and reduced by 0.4 days/week with saline; this was not statistically significant ($p=.084$)

- On secondary measures, none favored botulinum toxin treatment; however, days per week of sick leave increased with botulinum toxin by 0.5 days/week and decreased by 0.1 days/week with saline ($p < 0.001$ in favor of saline)
- Adverse effects of botulinum toxin were mild or moderate and resolved within 4 weeks of injection

Authors' conclusions:

- The use of botulinum toxin for cervicogenic headache is not supported by the study results
- This failure may be due to the fact that cervicogenic headache is not mediated by neurogenic inflammation, and botulinum toxin inhibits the release of mediators of neurogenic inflammation
- There is a lack of a clear "gold standard" for cervicogenic headache; most patients with a diagnosis of cervicogenic headache do not have demonstrable neck lesions
- It is doubtful that a different injection regimen such as a follow-the-pain strategy would have been an improvement over the standardized injection regimen used in this study
- Most patients had had headache for over a decade and were disabled by chronic pain, but the current results were not influenced by compensation demands, since litigation was an exclusion criterion
- There was not a true washout period; the potential duration of botulinum toxin effectiveness is not known, and a carryover effect from the active drug into the placebo period cannot be ruled out

Comments:

- Some of the potential limitations of the study (possible carryover effect of botulinum toxin into the placebo period, lack of a gold standard for diagnosis of cervicogenic headache) are discussed by the authors, but it is not clear that the fixed-site injection protocol accurately reproduces the likely use of botulinum toxin in clinical practice
 - o An unbiased study could have been done with injection sites tailored to individual patient pain patterns as long as blinding of the injector was maintained
- Occipital nerve block was a part of the screening criteria for entry, but the details are lacking (steroid/anesthetic dose and definition of a positive response)
- The response to both botulinum toxin and saline is reported for both 8-week periods combined, rather than separately for the group that received botulinum toxin first and received it second; this makes it more difficult to evaluate the possibility of a carryover effect
 - o The authors did report that there was no period effect (the effect of botulinum toxin did not depend on whether it was administered first or second); the reported combined data may be an unbiased approximation of the botulinum toxin effect

- Blinding is likely to have been successful, and major risks of bias appear to have been controlled
- Although there is some uncertainty in the measure of pain intensity response to treatment, the data in Table 1 on mean intensity of headache may be combined with the data in the Cochrane review (Langevin 2010) for cervicogenic headache

Assessment: Adequate for evidence that the effect of fixed-site injection of botulinum toxin for cervicogenic headache is not likely to be greatly different from placebo